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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,083	05/14/2001	Jean-Louis Ruelle	BM45332	5878

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EXAMINER
FORD, VANESSA L

ART UNIT	PAPER NUMBER
1645	10

DATE MAILED: 05/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,083	RUELLE, JEAN-LOUIS	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-38,45 and 51-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-38,45 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of Group I, claims 27-38, 45 and 51-53 without traverse in Paper No. 9 is acknowledged. Claims 39-44, 46-50 and 54-59 have been cancelled.

Claim Objections

2. Claims 45 and 51 are drawn to a cancelled claim. Applicant should amend the claims so that it is drawn to the elected invention.

Drawings

3. The drawings are objected to by the Draftsman under 37 CFR 1.84 or 1.152. See the attached form PTO 948.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 27-38, 45, and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 27-38, 45 and 51 are directed to isolated polypeptides selected from the groups consisting of a) an amino acid sequence which has at least 90% identity to SEQ ID Nos 2, 4, 6 or 8, an immunogenic fragment of the amino acid sequence of (a) wherein the immunogenic fragment is at least 90% identical to an aligned contiguous segment of SEQ ID Nos. 2, 4, 6 or 8 and an immunogenic fragment of the amino acid sequence of (a) that matches an aligned contiguous segment of SEQ ID No. 2,4, 6, or 8 which no more than five single amino acid substitutions, deletions or additions wherein the isolated polypeptide, when administered to a subject in a suitable composition which can include an adjuvant, or a suitable carrier coupled to the polypeptide, includes an immune response that recognizes a polypeptide having the sequence of SEQ ID Nos. 2,4,6 or 8.

The specification is enabling only for the polypeptides of SEQ ID NOs: 2,4,6 and 8 as disclosed in the specification. The specification states that "variant refers to a polynucleotide or polypeptide that differs from a reference polynucleotide or polypeptide but retains essential properties" and "generally differences are limited that the sequences of the reference polypeptide and the variant are closely similar overall an in many regions are identical". The specification states "that a variant and reference polypeptide may differ in amino acid sequence by one or more substitutions, additions, deletions in any combination" and " that a substituted or inserted amino acid residue may or may not be encoded by the genetic code"(page 48). There is no guidance provided as to which amino acids can be added, deleted or substituted and still have the polypeptide retain its biological function. The scope of the claims is not commensurate

with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some polypeptides is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such polypeptides.

The claims of the instant application are not only drawn to isolated immunogenic polypeptides but are also drawn to fragments of the polypeptides, which comprise at least 15 amino acids. There is no guidance provided in the specification as how one would begin to choose "at least 15 amino acids". The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which the retain the biological activity if the intact protein; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choice is likely to be successful.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or

guidance is presented in the specification with respect to selecting other antigens having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptides that are variants of SEQ ID NOs: 2,4,6 and 8 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation to is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

5. Claims 52-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable how to use the claimed vaccine for protection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 52-53 are drawn to a vaccine comprising the polypeptide of claim 27 and a pharmaceutically acceptable carrier.

The specification fails to teach how to use the claimed vaccines for protection. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to a bacterial infection or disease induction. The specification states that "the dosage range required depends on the choice of peptide, the route of administration, the nature of the formulation, the nature of the patient's condition and the judgment of the attending practitioner" (page 40). The specification further teaches that rabbits were vaccinated intramuscularly with the purified recombinant BASB034 protein and the animals produced high antibody titers (pages 62-63, Example 5 and Figure 6).

The specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of treating bacterial infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced. The ability to reasonably predict the capacity of a single bacterial immunogen or

combinations of immunogens to induce protective immunity from *in vitro* antibody reactivity studies is problematic. Ellis *(Vaccines, W.B. Saunders Company, 1988, Chapter 29)* exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of a protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies"(page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an *in vitro* neutralizing antibody response fail to elicit *in vivo* protective immunity. Boslego et al (*Vaccines and Immunotherapy, Pergaman Press, 1991, Chapter 17)* teach a single gonococcal pillin protein wherein the protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

It is well known in the art that there are several different antigens from *Moraxella catarrhalis* (i.e. outer membrane proteins, lipooligosaccharides). It is also taught that since infections caused by *Moraxella* predominately occur on mucosal surfaces, the mucosal immune response is likely important as the first line of defense. Mucosal or surface antigen immune response would likely be important in the search for candidate vaccines (Kyd et al. 2000). It has also been recognized in the art that there is currently no vaccine to prevent *Moraxella catarrhalis* infections because of a lack of good animal models for the diseases, a lack of information about the protective antigens, a lack of *in vitro* correlates to immunity against *Moraxella catarrhalis* in humans and the

pathogenic mechanisms and host immune response to the pathogens has yet to be clarified (Chen et al. 1996; Gu et al, 1998, Hu et al. 2000; Samukawa et al 2000 and Kyd et al 2000). While studies have been shown that the outer membrane proteins can elicit bacterial antibodies, which promote bacterial clearance, the results have not lead to a predictable vaccine against infections caused by *Moraxella catarrhalis*. A similar situation exists with the development of lipooligosaccharides (LOS) based vaccines against infections caused by *Moraxella catarrhalis*. Clearly a great amount of experimentation would be necessary in order to develop an efficacious vaccine against *Moraxella catarrhalis* infections.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to developing a vaccine that would achieve a desire level of success when administered to a patient with a bacterial infection that is capable of treating that bacterial infection, 3) there are limited working examples which suggest the desired results of a vaccine against *Moraxella catarrhalis*,

4)the nature of the invention involved the complex and incompletely understood area of protective immune responses against *Moraxella catarrhalis* 5) the state of the prior art shows the lack of correlates to immunity with *Moraxella catarrhalis,* 6) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 34 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 34 recites "a fusion protein comprising the peptide of claim 27". It is unclear as to what comprises the fusion protein? Clarification is required.

7. Claims 35 and 37 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "the aligned sequence". It is unclear as to what the applicant is referring. Clarification is required.

8. Claims 45 and 51 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "conditions sufficient". It is unclear as to what the applicant is referring? Thus, the metes and bounds of "conditions sufficient" cannot be ascertained. Clarification as to the meaning of this term is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

It should be noted that the Examiner is viewing the recitation of "vaccine" as a pharmaceutical.

9. Claims 27-32, 34-38 and 52 are rejected under 35 U.S.C. 102(b) as anticipated by Sarwar et al *(Infection and Immunity, March 1992, p. 804-809).*

Claims 27-32, 34-38 and 52 are drawn to a polypeptide comprising a member selected from the group consisting of:

(a) an amino acid sequence which has at least 90% identity to SEQ IDS Nos: 2,4,6 or 8;

(b) an immunogenic fragment of the amino acid sequence of (a) wherein the immunogenic fragment is at least 90% identical to an aligned contiguous segment of SEQ ID Nos: 2,4,6 or 8 and

(c) an immunogenic fragment of the amino acid sequence of (a) that matches an aligned contiguous segment of SEQ ID Nos. 2, 4,6 or 8 with no more than five single amino acid substitutions, deletions or additions;

wherein the isolated polypeptide when administered to a subject in a suitable composition which can include an adjuvant, or a suitable carrier coupled to the polypeptide induces an immune response that recognizes a polypeptide having the sequence of SEQ ID Nos: 2, 4, 6 or 8.

Sarwar et al teach an outer membrane protein of *Moxarella catarrhalis* (formerly *Branhamella catarrhalis*) that has a mass of 55 kDa at room temperature and 60 kDa when heated under reducing conditions. Sarwar et al teach that the expression of epitopes is independent of growth phase and growth media and are highly specific for *Moxarella catarrhalis* (see the Abstract). Sarwar et al teach epitopes of the outer membrane protein of *Moxarella catarrhalis* (formerly *Branhamella catarrhalis*) that are recognized by two different antibodies, 5E8 and 7D6. Sarwar et al teach that the expression of epitopes is independent of growth phase or growth media (see the Abstract). Sarwar et al teach that the 5E8 epitope is expressed on the surface of the bacterium. Sarwar et al teach that the epitopes are highly specific for *Moxarella catarrhalis*, being absent from a variety of other gram-negative bacteria (page 808, 2nd column). Sarwar et al teach that antibody 5E8 was produced by immunizing BALB/c

mice subcutaneously with Zwittergent-extracted outer membrane of *Moxarella catarrhalis* in both complete and incomplete Freund's adjuvant (page 804, 2nd column). Sarwar et al suggest that the outer membrane of *Moxarella catarrhalis* may have a potential role as a vaccine antigen. The protein of the prior art is similar if not the same as for example, an amino acid sequence which has at least 90% identity to the SEQ ID NO:2 since they are both outer membrane proteins which have a molecular weight of about 60 kDa. The sequence of the outer membrane protein of *Moxarella catarrhalis* would be inherent in the teachings of the prior art.

Since the Office does not have the facilities for examining and comparing applicant's polypeptide with the polypeptide of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e.,that the polypeptide of the prior art does not possess the same material structural and functional characteristics of the claimed polypeptide). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Pertinent Prior Art

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure *(Murphy et al Infection and Immunity, October 1989, p. 2938-2941).*

Status of Claims

11. No claims are allowed.

Conclusion

12. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
May 9, 2002

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